CASE REPORT

Primary Liver Lymphoma in a Patient with Chronic Hepatitis C

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Primary liver lymphoma is a very rare disease and is frequently overlooked as a possible diagnosis. We report the case of an asymptomatic middle-aged man with chronic hepatitis C who developed primary liver lymphoma (PLL). A large solitary tumor in the left lobe of the liver was incidentally detected on routine ultrasound examination. Imaging studies showed mixed iso- and hypoechogenicity with hypoechoic rim, hypodense in the pre-contrast phase and thick wall enhancement in the post-contrast phase on computed tomographic study, hypointensity on T1WI, and hyperintensity of the central portion and slightly higher intensity in the peripheral wall on T2WI. These pictures were different from focal nodular hyperplasia, hepatocellular carcinoma, cholangiocarcinoma or metastases. Atypical hepatectomy was performed and the pathology of the hepatic tumor revealed non-Hodgkin's lymphoma. Systemic staging revealed no evidence of nodal or bone marrow involvement, so PLL was diagnosed. There was no tumor recurrence more than 4 years after operation and chemotherapy. PLL should be included in the differential diagnosis of solitary hepatic tumor in patients who are hepatitis C virus-positive, and who have atypical imaging and no known malignancy or elevated tumor marker levels. [*J Formos Med Assoc* 2006;105(3):242–246]

Key Words: hepatitis C virus, hepatic tumor, lymphoma, primary liver lymphoma

In Taiwan, hepatocellular carcinoma (HCC) is the leading cause of cancer death.[1] With advances in imaging technologies, HCC is no longer difficult to diagnose, particularly when alpha-fetoprotein (AFP) is elevated and the patient has chronic hepatitis B or C. However, primary liver lymphoma (PLL) is a very rare disease, with fewer than 150 reported cases,[2] and it is frequently overlooked as a possible diagnosis. PLL is not easily differentiated from other hepatic tumors or pseudotumors by imaging studies and clinical course. We describe the imaging features and their correlation with pathologic results and clinical course in an asymptomatic, middle-aged man with chronic hepatitis C who developed PLL.

Case Report

A 55-year-old man with a 4-year history of chronic hepatitis C underwent routine ultrasonographic follow-up, which disclosed a solitary and mixed iso- and hypoechoic mass with hypoechoic rim, about 7 cm in diameter, in the left hepatic lobe (Figure 1A). This mass had not been seen on follow-up 3 months previously. He had been well without any subjective symptom or noticeable weight loss. Physical examination did not reveal icteric sclerae, liver pain, vascular spiders on the skin or lymphadenopathy. Laboratory studies on admission showed the following results: aspartate aminotransferase, 35 IU/L (normal, < 37 IU/L);

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alanine aminotransferase, 49 IU/L (normal, < 41 IU/L); alkaline phosphatase, 134 IU/L (normal, 70–250 IU/L); absence of elevated tumor markers such as AFP (< 20 ng/mL), CA 19-9 (17 U/mL; normal, < 37 U/mL), prostate specific antigen (0.7 ng/mL; normal, < 4.0 ng/mL) and carcinoembryonic antigen (1.48 ng/mL; normal, 0–5 ng/mL); positive antibody for hepatitis C virus (HCV); negative HBsAg and anti-HBs. An abdominal computed tomography (CT) scan demonstrated that the tumor was hypodense in the pre-contrast study and had thick wall enhancement in the post-contrast study (Figure 1B). Magnetic resonance imaging (MRI) showed hypointensity in relation to the liver on T1-weighted imaging (WI), hyperintensity of the central portion on T2WI and slightly higher intensity in the peripheral wall (Figure 1C). After Gd-DTPA administration, there was rim enhancement between the central low intensity portion and relatively hypointense peripheral wall

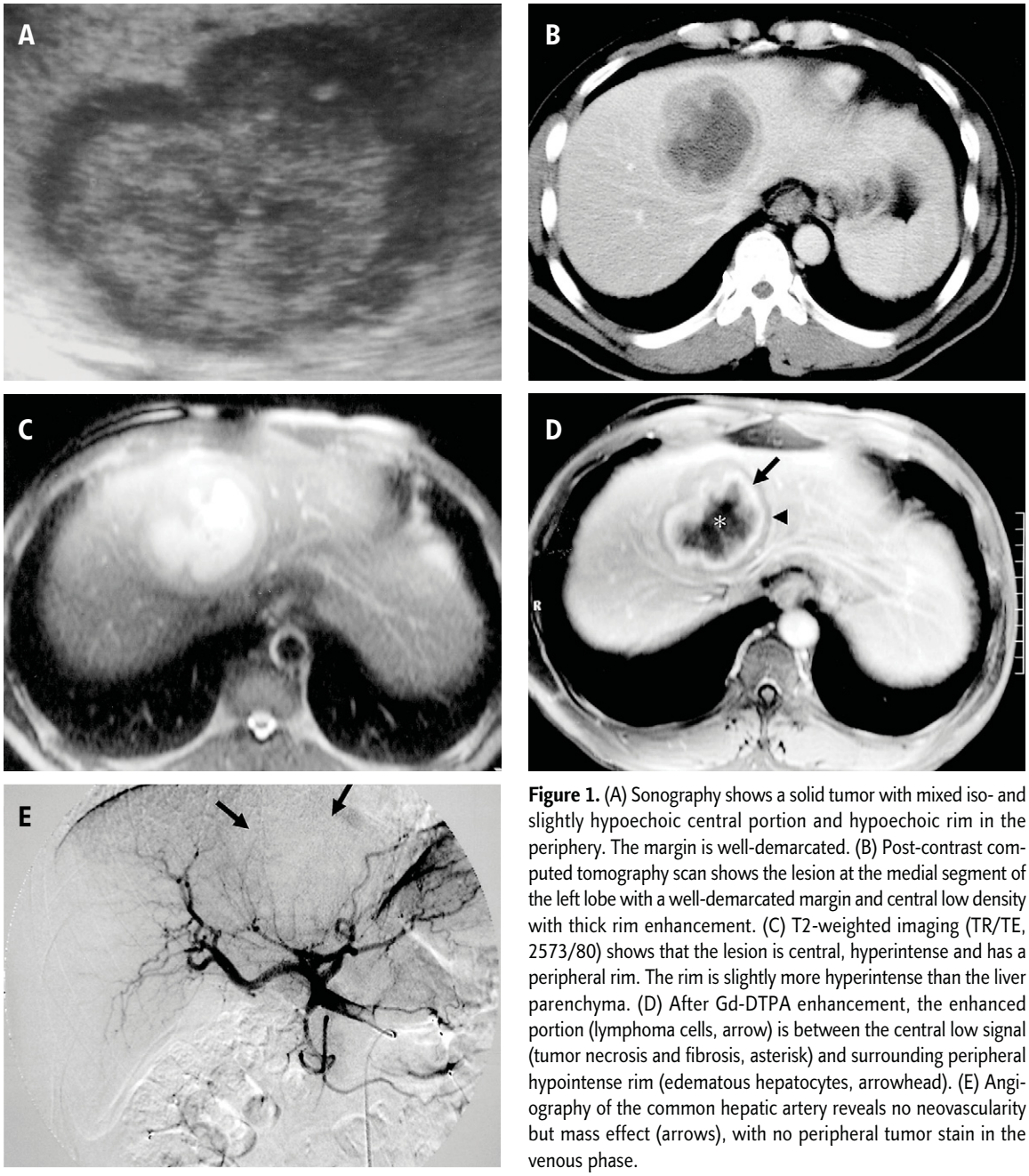

Figure 1. (A) Sonography shows a solid tumor with mixed iso- and slightly hypoechoic central portion and hypoechoic rim in the periphery. The margin is well-demarcated. (B) Post-contrast computed tomography scan shows the lesion at the medial segment of the left lobe with a well-demarcated margin and central low density with thick rim enhancement. (C) T2-weighted imaging (TR/TE, 2573/80) shows that the lesion is central, hyperintense and has a peripheral rim. The rim is slightly more hyperintense than the liver parenchyma. (D) After Gd-DTPA enhancement, the enhanced portion (lymphoma cells, arrow) is between the central low signal (tumor necrosis and fibrosis, asterisk) and surrounding peripheral hypointense rim (edematous hepatocytes, arrowhead). (E) Angiography of the common hepatic artery reveals no neovascularity but mass effect (arrows), with no peripheral tumor stain in the venous phase.

(Figure 1D). No abnormal lesion was detected in other body organs by preoperative diagnostic imaging techniques. Hepatic angiography showed no significant neovascularity but mass effect (Figure 1E). Endoscopic examinations of the upper and lower gastrointestinal tracts were performed but no abnormality was found.

Because of the rapid growth rate of the tumor and absence of primary focus, surgical exploration was performed and atypical hepatectomy was undertaken. The frozen section revealed a malignant lymphoma; subsequently, splenectomy and intra-abdominal lymph node biopsy were performed. Grossly, the hepatic mass was a well-defined, non-encapsulated, grayish white and soft tumor, measuring 7.5 × 7 × 7 cm (Figure 2A). Central scarring and necrosis were also noted. The non-tumor part of the liver parenchyma showed no cirrhosis and was not remarkable. Microscopically, the tumor cells were large with plasmacytoid or immunoblastic appearance (Figure 2B), and the margin of the tumor was ill-defined. Immunohistochemical staining of the tumor tissue was positive for CD20 and leukocyte common antigen (LCA, CD45), but negative for CD3. Thus, non-Hodgkin's diffuse large cell, immunoblastic type, B-cell lymphoma was diagnosed. The central part of the tumor showed sclerotic change without tumor cells. The spleen showed follicular hyperplasia of white pulp with polymorphous lymphoplasma cells and occasional immunoblastic infiltration. The lymph node showed the same follicular hyperplasia and plasma cell infiltration.

Systemic staging revealed no evidence of nodal or bone marrow involvement, so primary liver lymphoma was diagnosed. The patient received four courses of combination chemotherapy postoperatively, which consisted of cyclophosphamide, epirubicin, vincristine, and oral prednisolone (CEOP). At the last follow-up 4 years after the operation, he was well without any sign of recurrence.

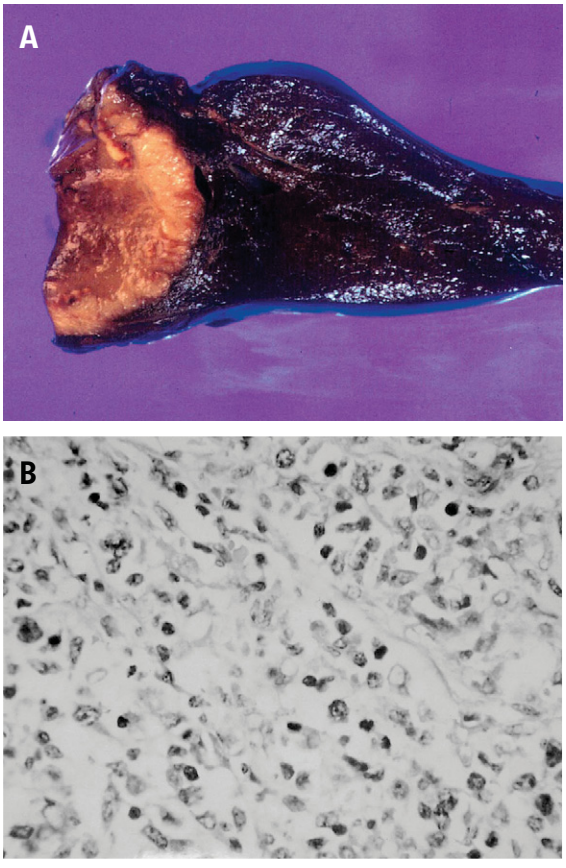

Figure 2. (A) The hepatic mass is a well-defined, non-encapsulated, grayish white and soft tumor. Central scarring and necrosis are also noted. (B) Pathologic section shows that the tumor cells are large with plasmacytoid or immunoblastic appearance, and immunohistochemistry reveals diffuse large B-cell lymphoma of the immunoblastic type.

Discussion

PLL is defined as an extranodal lymphoma of the liver without involvement of any other organ. It is a rare condition which is frequently overlooked as a possible diagnosis. In Taiwan, HCC is the most common primary malignant hepatic tumor,[1] and is always suspected first, especially in a patient who is an HBV or HCV carrier. Morphologically, HCC may appear as solitary, multiple nodules or diffusely infiltrative and almost hypervascular.[3] The typical features of HCC include hyperattenuation at the early arterial phase of CT scan and angiography.[4] Larger HCC (> 5 cm in diameter) sometimes show hypoattenuation within the central portion of the tumor on early CT phase, but most are hypervascular on angiography.[4] Although some hypervascular HCC may be undetected on CT or angiography, most undetected tumors are smaller (< 3 cm).[4] Furthermore, among patients with HCC without elevated AFP, the reported percentage of tumors > 5 cm is low, ranging from only 16% to 25%.[5,6]

Common hypovascular tumor should be included in the differential diagnosis of patients with solitary liver tumor detected on routine imaging, including the mass-forming peripheral type of cholangiocarcinoma, metastatic tumors and, less commonly, lymphoma. Cholangiocarcinoma arises from the bile duct epithelium and the most common appearance of the peripheral type on images is a lobulated, predominantly hypoattenuated mass in the central portion appearing as fibrosis and hyperattenuated enhancement in the periphery with focal dilatation of intrahepatic ducts.[7,8] However, the tumor in our patient had a regular border without intrahepatic duct dilatation. Metastatic tumor with central necrosis, especially colon cancer, was also suspected in our patient, but no primary cancer was found on subsequent clinical examinations.

Benign lesions, such as abscess and focal nodular hyperplasia (FNH), should also be included in the differential diagnosis of patients with solitary hepatic lesions. FNH is iso- or hypointense on T1WI, slightly hyper- or isointense on T2WI, and shows vivid signal homogeneity during the early phase of dynamic contrast enhancement.[9] Central scar appears hyperintense on T2WI and with enhancement on the delayed phase after contrast medium administration,[9] but the image of our patient showed central low signal without significant enhancement. Abscess is another hypovascular hepatic tumor that should be included in the differential diagnosis of patients with solitary hepatic lesions. A well developed abscess may have a thick wall that engulfs the fluidic central portion. In our patient, the pattern of CT and MRI was very similar to this condition;[10] however, it was excluded by the clinical finding of lack of infectious signs.

The least likely tumors that should be included in the differential diagnosis of solitary liver lesions are unusual liver tumors such as lymphoma. In our patient, pathology revealed diffuse immunoblastic large B-cell malignant lymphoma. Widespread non-Hodgkin's lymphoma often involves the liver, but PLL is very rare.[2] Review of the reported cases[2,11–14] reveals that PLL should be included in the differential diagnosis if the clinical condition and imaging picture are not typical. The most common picture of PLL is a solitary and well-defined tumor, but multiple nodules and/or diffuse infiltrative form may also be found as the presentation of secondary liver lymphoma.[13] The imaging features of most PLL, as in the present case, are iso- to hypoechoic on sonography, hypodense on pre-contrast, and show rim enhancement on post-contrast enhanced CT.[9,12–14] MRI shows similar findings with Gd-DTPA enhancement; however, three layers of different tissue characteristics are more clearly demonstrated on MRI. Correlated with the pathologic findings, the central part of this tumor has dominantly sclerotic change without viable tumor cells; the prominent enhanced portion at the intermediate layer is chiefly the lymphoma cells; the outermost layer is comprised of compressed and edematous hepatocytes (Figure 1D).[12,13] Little vascularity is seen on angiography, but mass effect is evident (Figure 1E). These angiographic findings are suggestive of tumors other than hypovascular HCC,[4] cholangiocarcinoma[7,8] or metastasis because peripheral tumor stains or faint neovascularity are usually present in a large-sized tumor. After exclusion of the more common tumors, therefore, PLL should be included in the differential diagnosis even though it is rare.

Hepatitis C is another indicator of the need to include PLL in the differential diagnosis of solitary tumors. The prevalence of HCV infection was higher in patients with B-cell non-Hodgkin's lymphoma than in controls.[15,16] Mizorogi et al also reported that primary liver involvement was detected in three of 17 HCV-positive patients, but in none of 83 HCV-negative patients.[16] The frequent association with HCV suggests that this virus may play a role in the pathogenesis of PLL. The evolution from a benign cryoglobulinemia to a malignant B-cell lymphoma of lymphoplasmacytic type has been reported.[17] Ferri et al proposed that HCV acts as a triggering factor for immune activation and can lead to benign or malignant lymphoproliferative disorders.[18] Although HCV has been shown to be lymphotropic, HCV RNA genomic se-

quences cannot integrate into the host genome, which has led to consideration of an indirect mechanism of malignant transformation.[17] Malignant lymphoma in HBV carriers was also reported, but the relationship of HBV and lymphoma is considered to be independent.[19] Scoazec et al suggested that several characteristics of PLL form a rather uniform clinical picture, but the viewpoint that it is a slow progressing disease may be wrong.[20] They considered PLL to be the same as other lymphomas with rapid tumor growth, such as in our patient whose hepatic tumor grew rapidly over a 3-month period. The best treatment for PLL remains unclear, with some clinicians using surgery only, while some prefer chemotherapy alone or combined with radiotherapy. However, Page et al considered that surgery alone does not appear to be sufficient therapy in view of early extrahepatic recurrence, and combination chemotherapy is probably the most appropriate treatment.[21]

In conclusion, PLL is rare and frequently overlooked as a possible diagnosis in patients with a solitary hepatic lesion. Our patient was an HCV-positive middle-aged male patient without known malignancy or elevated levels of tumor markers, a set of clinical conditions that should lead to increased suspicion of PLL in the differential diagnosis of solitary hepatic tumor. The combination of sonography, CT, MRI and angiography may be useful in distinguishing PLL from other tumors.

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